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CASE REPORT

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# Anti-GAD Encephalitis Following COVID-19 Vaccination: A Case Report

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## ABSTRACT

Since December 2020, a significantly higher number of people worldwide have been vaccinated for coronavirus disease 2019 (COVID-19). Neurological complications have been reported after these vaccines, although a definitive causal relationship has not been proven in the available literature. We describe a 51-year-old man presenting with anti-glutamic acid decarboxylase (anti-GAD) antibody positive autoimmune encephalitis with progressive cognitive impairment and behavioral abnormalities, presenting shortly after the second dose of mRNA COVID-19 vaccine, possibly representing a serious vaccine-related adverse event. Response to high-dose steroid and intravenous immunoglobulin treatment was positive. As many people around the world have been vaccinated against COVID-19, this case shows that autoimmune encephalitis and even anti-GAD antibody positive autoimmune encephalitis can develop as a side effect after this new vaccine, but with early diagnosis and appropriate treatment, the clinic can have a good prognosis. Observational studies with large numbers of patients are needed to explain causality.

**Keywords:** anti-GAD encephalitis, autoimmune encephalitis, COVID-19 vaccination

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## INTRODUCTION

Autoimmune encephalitis (AE) is a rare inflammatory neurological condition associated with autoantibodies. It is characterized by new onset seizure, cognitive impairment, and psychiatric symptoms. Anti-glutamic acid decarboxylase (GAD), anti-N-methyl-d-aspartate-receptor (NMDAR), anti-voltage-gated potassium channels (VGKC) complex and anti-γ-aminobutyric acid receptor antibodies are the most frequently reported antibodies that can cause different clinical manifestations of AE (1).

Anti-GAD antibodies have been demonstrated in a variety of neurological syndromes across heterogeneous clinical conditions such as limbic encephalitis, cerebellar ataxia, and stiff person syndrome. Anti-GAD positive limbic encephalitis often manifests with a prodrome of nonspecific neurological and neuropsychiatric symptoms that may include headache, irritability, delusions, hallucinations, psychosis, and short-term memory impairment (2). Furthermore, some studies have reported the association of anti-GAD antibodies with epilepsy and status epilepticus, including epilepsia partialis continua (3).

In Turkey, the mRNA vaccine Comirnaty (also known as BNT162b2; Pfizer/BioNTech) has been granted emergency authorization and introduced for use by the Ministry of Health in April 2021 for prevention against the novel coronavirus disease 2019 (COVID-19). Published safety and efficacy trials of messenger ribonucleic acid (mRNA) vaccines have reported high efficacy rates up to 94–95% after two interval doses with limited side effects and a low rate of adverse reactions (4). The vaccine-related autoimmune conditions reported in the literature include Guillain-Barré syndrome, acute disseminated encephalomyelitis and cerebellitis (5–7).

In this study we aimed to report and discuss a case of anti-GAD antibody positive limbic encephalitis who presented with neuropsychiatric symptoms and non-convulsive status epilepticus shortly after the mRNA vaccine administered for COVID-19.

### Highlights

- **Autoimmune encephalitis (AE) related with Covid-19 vaccination is rare.**
- **A case of anti-GAD Ab positive AE is presented.**
- **An accurate differential diagnosis is important in cases of AE.**
- **Early treatment provides a favorable prognosis in these cases.**

## CASE

A 51-year-old male patient was admitted to our clinic due to cognitive difficulties and behavioral abnormalities. It was learned in history that the second dose of the COVID-19 mRNA vaccine was administered 20 days priorly. On the third day of vaccination, redness in the right eye, headache, nausea, and vomiting occurred. Later, pauses in speech, meaningless answers to questions, self-talk, audio-visual hallucinations, insomnia, and memory impairment started to accompany these complaints. Oral diphenylhydantoin 300 mg/day treatment was started because of the recurrent clonic focal motor seizures localized in the right side of the face, neck and arm on the 17th day, in another neurology clinic. Neuroimaging and blood tests of the patient were considered to

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be unremarkable. As the clinical status continued to worsen, the patient was admitted to our clinic for further examination and treatment. No psychiatric, neurological, or systemic disease was described.

His neurological examination revealed confusion and decreased verbal fluency, on admission. Cranial nerve examination was unremarkable. His muscle strength was normal and low-amplitude tremor triggered by movement was detected in both hands. There was no fever or sign of meningeal irritation. No significant abnormality was detected in the examination of respiratory, cardiovascular, or other system examinations.

Electroencephalography (EEG) revealed abnormal background activity with generalized continuous 1–1.5 Hz delta activity predominant in fronto-temporal regions. This activity returned to normal after pharmacological treatment with 10 mg IV diazepam (Figure 1 and 2), without clinical improvement. Magnetic resonance imaging (MRI) of the brain revealed multiple lesions with hyperintense signal enhancement in both hemispheres predominantly in the bilateral temporal-medial regions on T2 and FLAIR-weighted (fluid attenuated inversion-recovery-weighted) sequences. There was no hemorrhage or contrast enhancement (Figure 3 a–c). Cerebrospinal fluid (CSF) examination revealed lymphocytic pleocytosis (150 cells/mm$^3$) with a high protein level (65.5 mg/dL). The CSF meningitis/encephalitis panel (bacterial and viral), CSF and blood cultures were negative. Cerebrospinal fluid IgG index was 0.61 mg/Dl, oligoclonal band (OCB) was type 4 positive. Myelin oligodendrocyte glycoprotein antibody (MOG-IgG) tested in CSF and serum was negative. The paraneoplastic panel (Anti-Hu, Anti-Yo, Anti-Ri, Anti-amphiphysin, Anti-Tr, Anti-PCA-2, Anti-Ma, Anti-CV2.1, Anti-ANNA-3) of the serum sample was negative, and the autoimmune panel analyzed using the CSF sample was positive for anti-GAD antibody (183.6IU/mL). No pathological features were found in thoracal and abdominal computerized tomography (CT) examinations.

On admission EEG was interpreted as non-convulsive status epilepticus according to Salzburg criteria (8). Since he had been on oral diphenylhydantoin 300 mg/day treatment for three days, we added 3000 mg/day/IV levetiracetam treatment with a loading dose. Due to the possibility of HSV encephalitis, IV acyclovir 2250 mg/day treatment was also started. None of the clinical and EEG findings improved on the second day of treatment. Upon the interpretation of the patient's clinical and MRI findings in favor of limbic encephalitis, methylprednisolone (1000 mg/day) and intravenous immunoglobulin (IVIG) (2 gr/kg/week) treatment was started. We also stopped diphenylhydantoin and added 200 mg/day oral lacosamide as a second antiepileptic agent. On the fourth day, the patient regained partial orientation and cooperation, and on the tenth day, the clinical condition was completely normal. Acyclovir

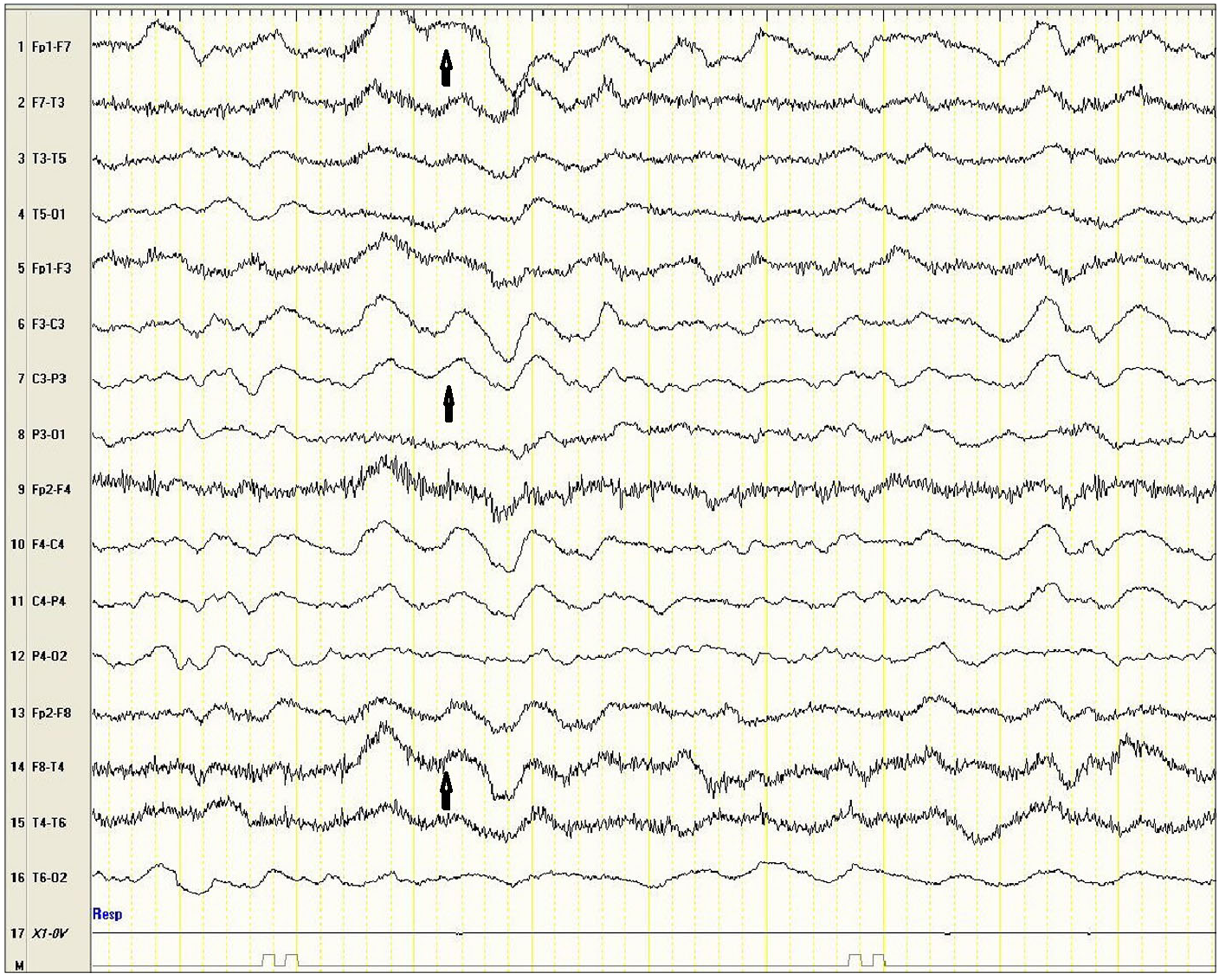


**Figure 1.** Electroencephalography samples showing continuous, rhythmic 1–1.5 Hz, generalized, delta wave activity prominent in the frontotemporal regions **(arrows).**

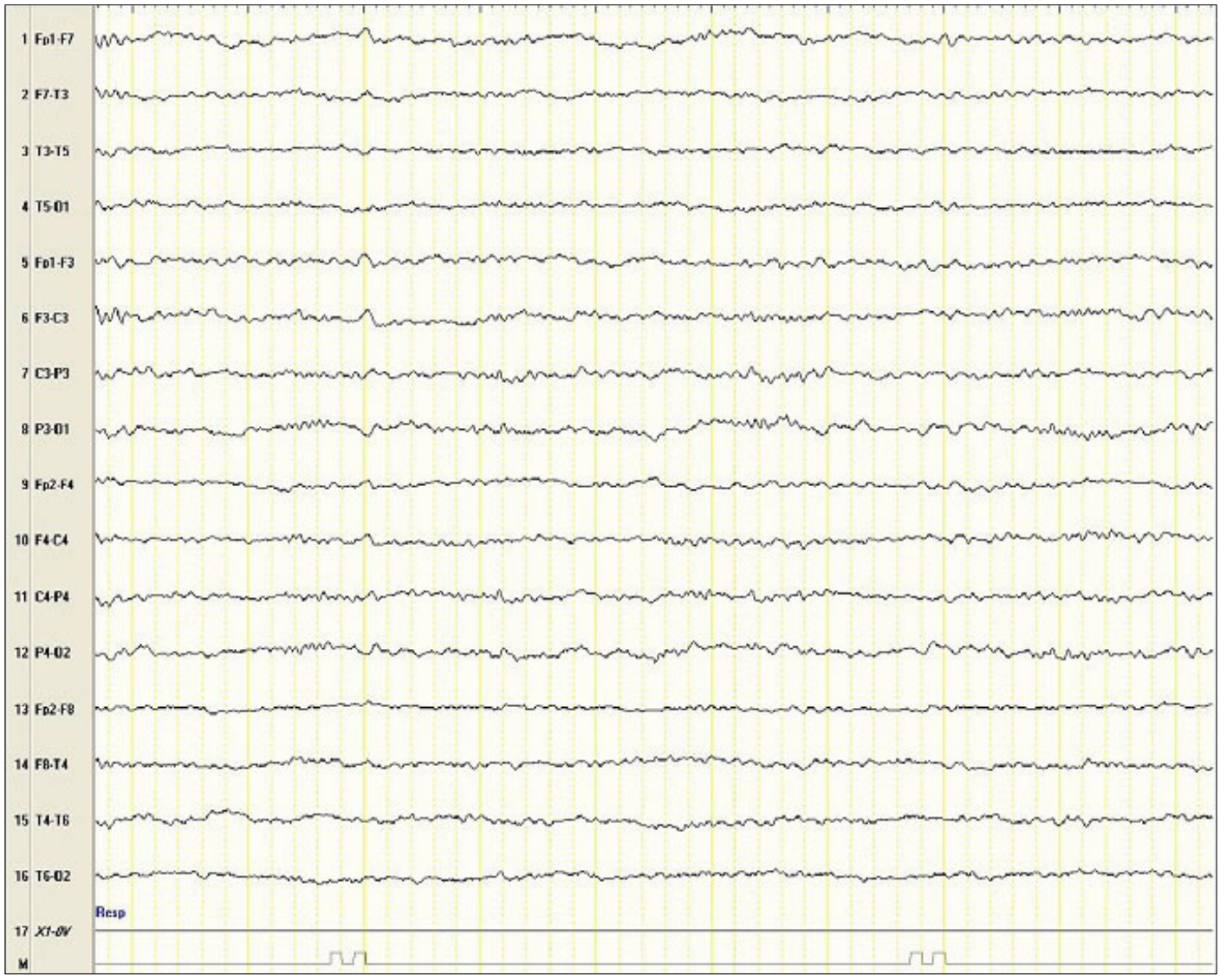


**Figure 2.** Electroencephalography findings improved significantly after diazepam infusion.

treatment was discontinued on the 7th day due to negative HSV test results in CSF and serum. Oral methylprednisolone was discontinued in four weeks' time with a tapering dose. On the first month of follow-up, neurological examination was normal, except the low-amplitude tremor in both hands. Electroencephalography examination revealed mild slow background activity in bilateral temporal areas. Regression was detected in T2 and Flair hyperintense lesions in brain MRI (Figure 3 d–f). Cerebrospinal fluid examination was acellular and protein level was within normal limits. He got monthly intravenous immunoglobulin (0.4 gr/kg/day) for three months. On the fourth month of follow-up cognitive difficulties in memory and perception occurred. No epileptiform activity was observed in EEG examination, and background activity was normal. In brain MRI increase in T2 hyperintense lesion load was observed (Figure 3 g–i). Cerebrospinal fluid examination was acellular and protein level was in normal limits. The patient was treated with methylprednisolone 1 gr/day for 10 days and intravenous immunoglobulin 0.4 gr/kg/day for 5 days. Clinical improvement occurred on the fifth day of therapy. We planned rituximab treatment with oral methylprednisolone for prophylaxis.

Written informed consent was obtained from the individual (s) for each interventional procedure performed in this study and for the publication of any potentially identifiable images or data contained therein.

## DISCUSSION

In this study, a male patient who presented with cognitive impairment and behavioral changes, whose EEG examination supported a non-convulsive state, and who was diagnosed with anti-GAD associated AE with imaging and laboratory examinations is presented.

In differential diagnosis of patients with clinical features of limbic encephalitis, viral causes, especially HSV encephalitis, should be ruled out. MRI, EEG and CSF examinations guide the clinician in reaching the diagnosis. In autoimmune limbic encephalitis, diffusion restriction is mostly absent, hemorrhage is not seen, and contrast enhancement is less common in MRI. Fredriksen et al. evaluated the MRI examinations of 19 anti-GAD AE patients and reported abnormal hippocampal signal (26%), cortical/subcortical parenchymal T2 hyperintensity (37%), and parenchymal atrophy (47%) as the most related imaging findings. Abnormal parenchymal/leptomeningeal contrast enhancement was not observed in any of these patients. In herpes encephalitis, diffusion restriction may be detected on MRI in the early period, hemorrhage may occur in the subacute stage and mild, patchy contrast enhancement may be seen (9). Pleocytosis and protein increase in CSF can be seen in both viral and autoimmune encephalitis. After a viral cause has been ruled out by polymerase chain reaction (PCR) and serology, the clinician

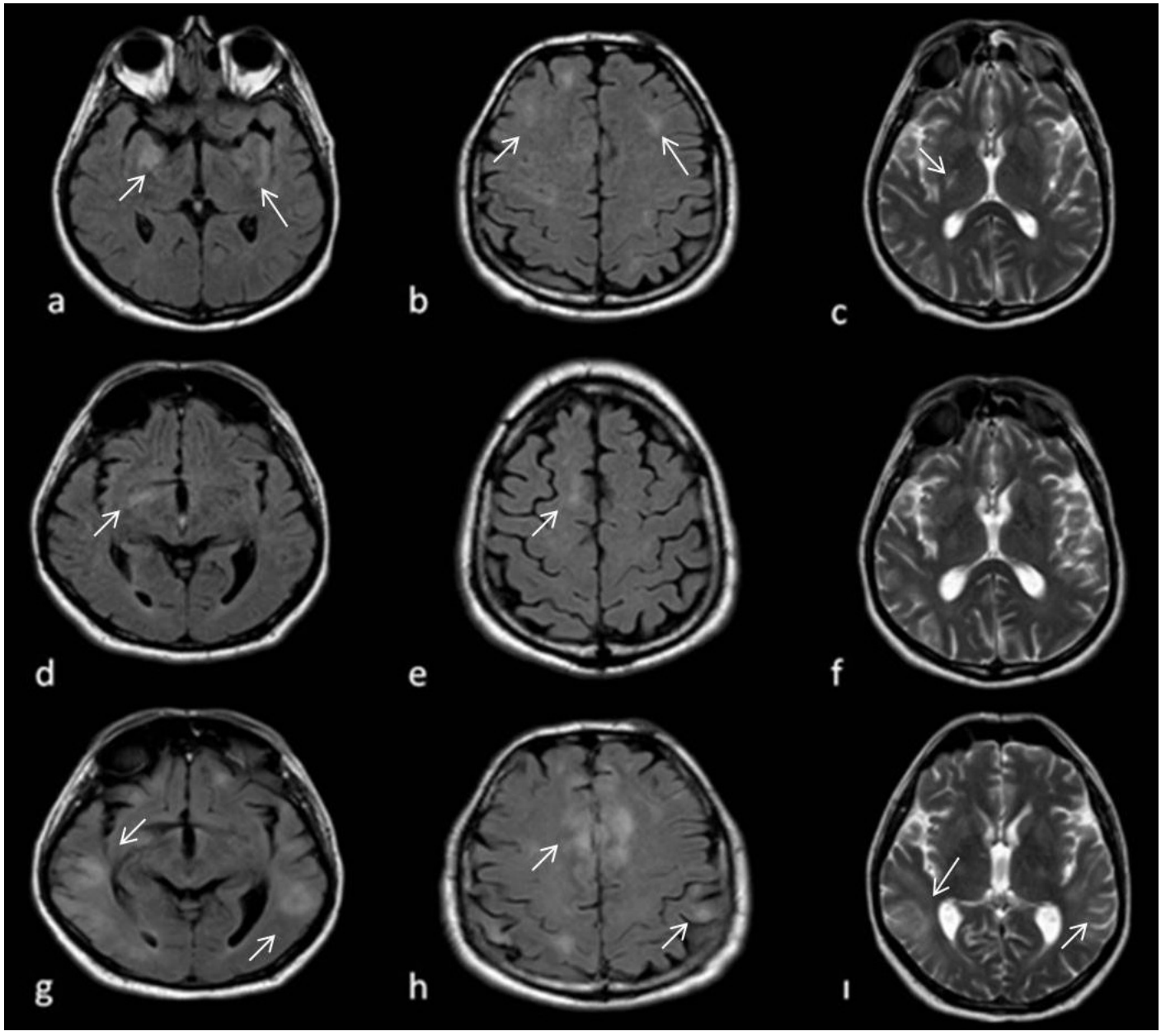


**Figure 3. a–c.** Magnetic resonance images taken at the first admission of the patient. Hyperintense signal in the medial aspect of bilateral temporal lobes in axial FLAIR sequence **(a).** Hyperintense signal in cortical regions in axial FLAIR sequence **(b).** Subcortical hyperintense signal in axial T2-weighted image **(c).** Magnetic resonance imaging findings at the 2nd month, when the lesions regressed after treatment **(d, e, f).** Magnetic resonance images of the 4th month relapse period in which the increase in cortical and subcortical lesions is observed in axial T2-weighted and FLAIR sequence **(g,h,i) (arrows).**

should determine the autoimmune etiology and whether the condition is paraneoplastic or not. Also, OCB's may be observed in AE (10). In diagnosis of AE in this patient, we followed procedure mentioned above. Glutamic acid decarboxylase antibodies have often been associated with limbic encephalitis and temporal lobe epilepsy. Like the other types of limbic encephalitis, GAD-associated limbic encephalitis is characterized by subacute onset seizures (53%), anterograde amnesia (67%), confusion and behavioral changes (30%). Although almost all patients experience seizure, non-convulsive status is rarely reported in this setting (11). Cognitive and behavioral changes in this patient may be due to both the involvement of the inflammatory process in the limbic system and the effect of the non-convulsive epileptic process. We think that the nonconvulsive state in this patient emerged due to autoimmune encephalitis and similar clinical findings potentiated each other. Because difficulties in cognition and behavior started ten days before the seizure onset and persisted despite antiepileptic therapy, mental difficulties resolved later than the EEG findings, and the second relapse on the fourth month presented with cognitive impairment without seizure activity. The dramatic response to immune therapies such as high-dose steroids and intravenous immunoglobulin also suggests the existence of an underlying autoimmune process.

It is noteworthy that the patient we presented here previously had a COVID-19 vaccination. Encephalitis is one of the neurological complications of COVID-19 infection (12). Therefore, in this case, we initially ruled out the COVID-19 infection itself. In literature, although so rarely reported, we could find possible AE cases presenting after COVID-19 vaccination (13). In only one patient, the diagnosis of AE was confirmed by positive leucine-rich glioma inactivated 1 (LGI1) antibody with CSF (13). We think that the relationship between COVID-19 vaccination and the development of autoimmune encephalitis should be interpreted very carefully, since so few cases with autoimmune encephalitis have been reported despite so many vaccinations worldwide. In general, vaccines can induce a strong expression of proinflammatory cytokines and a T-cell

response. Once stimulated, the immune system initiates a complex series of innate immune events that include phagocytosis; release of inflammatory mediators including chemokines and cytokines; and activation of the complement system and cellular recruitment. Circulating mediators and inflammatory products may affect other body systems to cause systemic side effects, and eventually, depending on the individual's immunogenetic background and innate immune memory, they may trigger microglia activation followed by neuroinflammation in some subjects (14,15).

In autoimmune encephalitis, first-line therapy consists of intravenous, high dose corticosteroids and IVIG or plasmapheresis (11). Data is lacking on which is optimum in this situation, so the choice is largely dictated by personal preference and experience. Early and effective treatment is important on the prognosis. To avoid further delay we preferred to use high-dose pulse steroid therapy in combination with IVIG in this patient. As the clinical improvement was satisfactory, we preferred to use monthly IVIG for prophylaxis. However, on the fourth month of follow-up, second relapse occurred. The clinical findings were noticed earlier and were milder. The frequency of clinical relapse in AE varies between 12% and 35% (16). Rituximab is generally effective in refractory cases and appears to reduce the risk of clinical relapse due to its increased use as initial therapy (16). Therefore, we planned rituximab for prophylaxis.

Limbic encephalitis is a rare condition, the underlying causes of which remain poorly understood. Due to the limited number of case reports following the administration of COVID-19 mRNA vaccines, the possible relationship has not been fully elucidated at this time. With this case report, we aimed to draw attention to autoimmune reactions and anti-GAD-related limbic encephalitis that may occur after vaccination. Early diagnosis and appropriate treatment are important to ensure a favorable prognosis.

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